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CASE REPORT

Sustained Complete Remission in a Patient with Platinum-Resistant Ovarian Yolk Sac Tumor

Alwin Jeyakumar, M.D., Eva Chalas, M.D.,* and Alexander Hindenburg, M.D.[1]

*Oncology/Hematology Division, Department of Medicine, and *Gynecologic Oncology, Department of Obstetrics and Gynecology, Winthrop University Hospital, Mineola, New York 11501*

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Background. **Yolk sac tumors of the ovary are generally very responsive to chemotherapy; however, they are difficult to manage in the setting of platinum resistance where treatment options are limited and outcomes are poorer.**

Case. **We present a 39-year-old woman who had a platinum-resistant yolk sac ovarian tumor. She achieved complete remission on an innovative regimen of docetaxel, gemcitabine, and thalidomide.**

Conclusion. **The combination of docetaxel, gemcitabine, and thalidomide might be an active regimen for platinum-resistant ovarian nondysgerminomas and further investigation of this combination is warranted.**

INTRODUCTION

We present a 39-year-old woman with platinum-resistant ovarian yolk sac tumor who achieved a sustained complete remission with a regimen consisting of docetaxel, gemcitabine, and thalidomide. This case illustrates activity of newer chemotherapeutic agents in the setting of platinum-resistant ovarian germ cell tumors, which remains a difficult clinical problem.

CASE REPORT

The patient is a 39-year-old woman who presented in July 1998 to another teaching institution with lower abdominal pain. On evaluation she was found to have a pelvic mass and in August 1998 underwent laparatomy with left salpingo-oophorectomy and pelvic sampling. Pathology revealed a 14-cm malignant mixed germ cell tumor with a predominantly yolk sac tumor component and contiguous left pelvic sidewall involvement, peritoneal washings were negative for tumor. She had optimal debulking surgery with no residual macroscopic disease; final stage was IIC. Preoperative α-fetoprotein (AFP) was elevated at 2400 ng/mL (normal: 0–9.1) and decreased to 1150 postsurgery.

She was advised to undergo chemotherapy, which she initially declined favoring alternative medical approaches; however, when seen again in October 1998 the AFP had risen to 16,322. She was given four cycles of etoposide and cisplatin (EP) on a 3-weekly schedule between October 1998 and January 1999. The doses used were cisplatin 50 mg/m^2 on Day 1 and etoposide 100 mg/m^2 on Days 1–3. There was a rapid decline in AFP to 42 and a negative follow-up CT scan of the pelvis; however, within 1 month, the AFP started to increase. She then started a regimen of vincristine, actinomycin D, and cyclophosphamide (VAC) in February 1999. Doses used were vincristine 1.5 mg/m^2 (maximum 2 mg) on Days 1 and 15, actinomycin D 0.35 mg/m^2 on Days 1–5, and cyclophosphamide 150 mg/m^2 on Days 1–5. There was a minimal decrease in AFP but significant vincristine-related peripheral neuropathy; hence only one cycle of VAC was given. Subsequently, she received four cycles of a monthly regimen containing cisplatin, etoposide, and ifosfamide (VIP) from March to June 1999. Doses given were cisplatin 20 mg/m^2, etoposide 100 mg/m^2, and ifosfamide 1200 mg/m^2 all on Days 1–5 with G-CSF support. The AFP decreased to 8 but within 2 months the AFP was 783, and she was advised to consider high dose chemotherapy with stem cell transplant as her next treatment option.

She declined this, sought several opinions, and transferred further care to our institution. In October 1999 after a CT scan of the pelvis showed new masses in the region of the left pelvic sidewall and uterus and an AFP of 4897, she underwent an exploratory laparatomy with radical cytoreductive surgery. Pathology revealed left adnexal, uterine, and omental involvement with tumor. Tumor samples were also sent for *in vitro* drug resistance assays (done at Impath labs, Irvine, CA) that indicated low intermediate resistance to carboplatin and low resistance to paclitaxel and gemcitabine. Postoperative AFP was 3186 and, while awaiting full records of prior chemother-

[1] To whom correspondence should be addressed at 200 Old Country Road, Suite 450, Mineola, NY 11501. Fax: (516) 663-4613. E-mail: alwinj@excite.com.

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apy, she received one cycle of carboplatin AUC-6 and paclitaxel 200/m^2 on November 17, 1999. However, 10 days later, AFP increased to 5900; a repeat value 5 days later was 6138 and a follow-up CT showed a new 2-cm right liver lobe mass. On December 9, 1999, she was started on a regimen of docetaxel 30/m^2 with gemcitabine 1000/m^2 on Days 1 and 8 of a 21-day cycle; a total of seven cycles were given from December 1999 to May 2000. In addition, thalidomide 200 mg daily was started on Day 1 of chemotherapy. She had immediate improvement in her AFP, which declined by the same velocity as its half-life of 5 days. By January 18, 2000 the AFP had decreased to 36 and has been in the normal range since February 10, 2000. On February 28, 2000, she underwent laparatomy with lysis of adhesions for recurrent symptoms of bowel obstruction; there was no evidence of tumor on biopsy specimens of mesenteric lymph nodes, small bowel adhesions, or peritoneal washings.

After five cycles of treatment, the AFP normalized and she was given two additional cycles of chemotherapy as consolidation; thalidomide at 200 mg daily was given for 1 year. She is now in sustained clinical and biochemical remission for more than 1 year with minimal residual sensory neuropathy. The most recent AFP on March 23, 2001 was 2.4 and the most recent CT scan on January 30, 2001 showed no evidence of disease.

DISCUSSION

Over the past decade, the treatment evolution of germ cell ovarian tumors has undergone major changes, largely as a result of the advances made in the treatment of testicular cancer [1]. Currently postoperative chemotherapy with a bleomycin/etoposide/cisplatin (BEP) regimen is the standard of care for all stages of germ cell ovarian tumors except stage IA dysgerminomas and stage IA grade I pure immature teratomas, where surgery alone is acceptable [2]. Good response rates are noted, with almost all patients cured in early-stage disease [2], and several trials show 60–80% long-term survivors with advanced disease [3]. There are studies that have shown four cycles of EP to be equivalent to a five-drug bleomycin-containing regimen in patients with good risk germ cell tumors [4]. Carboplatin has been looked into as an alternative agent to cisplatin in good prognostic metastatic nonseminomatous germ cell tumors where it is found to be effective but inferior to cisplatin [5]. Patients with residual poor-risk and advanced disease should be treated with four cycles of BEP given in full doses and on schedule, as dose reductions and delays in treatment have been associated with a compromise in outcome.

In patients who have persistent, progressive or recurrent disease after initial chemotherapy, treatment options depend on whether disease is platinum sensitive or resistant. Patients who relapse more than 6–8 weeks after completing platinum based chemotherapy are considered sensitive to platinum, whereas those who recur earlier are considered resistant to platinum [1–3]. Platinum-sensitive patients are given an alternative platinum regimen such as VIP or VeIP (vinorelbine, ifosfamide, and cisplatin), which can achieve a disease-free status in approximately 50% of these patients [6].

With platinum resistance, a non-platinum-based treatment regimen is considered such as VAC; however, these patients have less favorable outcomes. High-dose chemotherapy with stem cell transplant is another treatment option for platinum-resistant disease; however, several studies have shown that there is significant toxicity in this group of patients and only about 15% of these patients are cured [7].

Other agents have also been looked into in the setting of relapsed and platinum-resistant disease. Single-agent paclitaxel in phase II studies has been used for salvage treatment in germ cell tumors with a response rate of 26% demonstrated by Motzer *et al.* [8]. There are ongoing studies of paclitaxel use in combination therapy with other new agents. Gemcitabine has also shown activity in refractory germ cell tumors; Einhorn *et al.* demonstrated a 15% response rate in a heavily pretreated germ cell tumor patient population [9]. There is also a case report of a patient with stable partial response for more than 5 months after gemcitabine use in the setting of a platinum-resistant ovarian germ cell tumor [10]. Preclinical evidence also supports activity of docetaxel in paclitaxel-resistant cell lines [11, 12].

The combination of docetaxel and gemcitabine has been studied in combination in several different treatment settings. This appears to be a well-tolerated regimen without major toxicity and has been shown to be active in a variety of solid tumors including non-small cell lung cancer and bladder cancer [13]. Thalidomide is an inhibitor of tumor necrosis factor α (TNF); it is believed to exert an antitumor effect through both inhibition of angiogenesis and other antitumor mechanisms including enhanced cell-mediated immunity by direct stimulation of cytotoxic T cells [14]. Similar to other cytostatic agents, it has optimum efficacy if given daily and over a long period. Phase II studies have shown it to have activity in advanced renal carcinoma and to be of symptomatic benefit in other solid malignancies [15].

Our patient at the time of chemotherapy initiation had an AFP of 16,322; this value placed her in the poor-prognosis/high-risk group. She also likely had measurable metastatic disease at this time though this was not documented as she proceeded to chemotherapy without repeat imaging studies. Instead of treatment with the standard BEP regimen, she received four cycles of EP (usually given in good-risk patients [5]); also, EP in the doses given was grossly inadequate. It is entirely possible that inadequate initial chemotherapy contributed to the development of cisplatin resistance subsequently in this patient. It is unclear if subsequent AFP increase strictly represented initial platinum resistance, especially as it appears that she had a longer AFP response with four more cycles of platinum based therapy (VIP). On failing repeat platinum-based therapy, she was seen at our institution and had salvage

surgery, which has been described to be of benefit in a select group of patients with chemorefractory ovarian germ cell tumors [16]. Tumor tissue samples were sent for *in vitro* drug resistance assays; this has been used with variable success to determine drug resistance and hence eliminate the use of certain chemotherapeutic agents in ovarian cancer treatment. Following surgery, one cycle of carboplatin with paclitaxel was given; however, rapid progression was documented on the basis of a continuous rise in AFP and development of liver metastasis. This confirmed *in vivo* resistance to platinum and possibly paclitaxel and she was started on a regimen of docetaxel/gemcitabine/thalidomide. There was an immediate and dramatic treatment response and currently she remains disease free.

The initial very rapid decrease in AFP was likely due to the cytocidal effect of docetaxel and gemcitabine rather than the effect of thalidomide, which would be expected to have a much slower onset of action; however, a possible synergistic effect between the three agents cannot be ruled out. The sustained remission that was achieved may be secondary to the complete eradication of tumor by the induction regimen of docetaxel and gemcitabine. The contribution of thalidomide to maintenance of remission is yet to be determined.

CONCLUSION

This case report demonstrates that the combination of docetaxel, gemcitabine, and thalidomide might be an active and curative salvage regimen for platinum-resistant ovarian nondysgerminomas, resulting in complete and sustained remission. Further investigation of this combination is warranted.

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